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Original Article

Breast cancer therapy and age difference in cardiovascular disease risks: A population-based cohort study in Taiwan

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ABSTRACT

Objective: Cardiovascular events induced in breast cancer patients receiving radiotherapy (RT), chemotherapy (CT), or a combination of both (CRT) can increase the risk of death. This nationwide population-based study aims to estimate the risk of cardiovascular complications with a follow-up period of 5 years.
Materials and Methods: The study cohorts consisted of all patients hospitalized with a principal diagnosis of breast cancer who underwent treatment in 2002. The Cox proportional hazard model and Kaplan–Meier plot were analyzed to compare the cardiovascular event-free survival rate among breast cancer patients treated with different modalities.
Results: Of the 5514 breast cancer patients identified, 289 patients had cardiovascular disease (CVD): 110 (5.7%) from the surgery-alone group, 24 (4.1%) from the RT group, 79 (4.6) from the CT group, and 76 (5.8%) from the CRT group. Breast cancer patients who undergo CT and CRT at an age less than 55 years had a higher risk of CVD when compared with the surgery-alone group (for both groups, $p < 0.001$). By contrast, breast cancer patients aged over 55 years had no increased risk of CVD among the different treatment modalities.
Conclusion: : Breast cancer patients receiving CT and/or CRT have a higher risk of CVD, especially younger patients (aged < 55 years). Therefore, regular examinations of cardiac functions and electrocardiogram should be considered in cases of young breast cancer patients who are receiving CT and/or CRT.

Introduction

Breast cancer is the leading contributor to cancer mortality among women worldwide. Since 1990, the incidence and mortality rates of breast cancer have increased annually. At present, the incidence rate of breast cancer in Taiwan is approximately 59/100,000 [1]. Treatment for breast cancer includes surgical intervention and/or radiotherapy (RT), systemic treatment with cytotoxic chemotherapy (CT), hormone therapy, biologic therapy, or a combination of these (CRT) [2].

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Because of the anatomical location of the left breast, RT, which is a critical component of breast-conserving therapy for breast cancer, has been discussed a lot with ischemic heart disease in numerous studies [3–7,25]. However, caution must be exercised when extrapolating the results of this meta-analysis, which included older trials using outdated radiation techniques, to estimate risks for patients treated in the modern era.

Based on data in the Surveillance, Epidemiology, and End-Results (SEER) registries, the hazard ratio of cardiovascular disease (CVD) after receiving RT for women with left-side treatment was 1.5 in 1979, but there were no significant differences in rates of hospitalization for ischemic heart disease, valvular heart disease, conduction abnormalities, or heart failure between 1986 and 1993 [8].

At present, about one third of newly diagnosed cancers are amenable to breast conservation; adjuvant systemic treatment is recommended if a relevant reduction of the estimated risk of recurrence and death can be expected with an acceptable level of treatment-related adverse effects [9]. The use of anthracyclines, which are chemotherapeutic agents with cardiotoxicity, may be recommended for most breast cancer patients and especially for those with human epidermal growth factor receptor type 2 (Her-2)-positive disease [10]. A significant increase in carotid intimal thickness, myocardial perfusion, and laboratory risk factors of atherosclerosis in patients treated with anthracycline-based CT was reported previously [11]. However, the actuarial incidence of cardiovascular complications has not yet been clearly described in Taiwan. In addition, age plays a key role in the development of CVD, but it is scarcely discussed together with breast cancer patients in the related literature. In this study, we sought to determine the incidence of cardiovascular complications in breast cancer while considering different therapies and age stratification by utilizing the National Health Insurance Research Database (NHIRD) in Taiwan.

Materials and methods

Database

This study used data from the 2002–2007 NHIRD, which are published by Taiwan's National Health Research Institutes. The NHIRD covered the medical benefit claims for approximately 97% of the Taiwanese population, and contains a registry of board-certified physicians and contracted medical facilities. However, this database does not contain information on tobacco use, dietary habits, and body mass index. Because these data consist of deidentified secondary data released to the public for research, this study was exempted from a full review by the Institutional Review Board.

The study cohort consisted of patients with breast cancer [identified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 174.0–174.9] aged 20 years or older diagnosed in 2002 who had undergone surgery, RT, CT, CRT, or surgery with adjuvant therapy. Patients with any type of CVD, including ischemic heart disease (ICD-9-CM 410–414) and congestive heart failure (ICD-9-CM 428), diagnosed before or during the index admission were excluded. We identified 5514 patients with breast cancer.

Measurements

The primary dependent variable in the study was CVD. We utilized administrative data to identify all patients who developed any type of CVD—ischemic heart disease (ICD-9-CM 410–414) and congestive heart failure (ICD-9-CM 428). Each breast cancer patient was traced back from the initial hospitalization date since 2002 to the end of 2007. CVD-free survival time was then calculated, with cases censored if the patient died from noncardiovascular causes during the follow-up period. We compared the outcomes for patients who underwent surgery alone, RT with or without surgery, CT with or without surgery, and CRT with or without surgery. The four groups were analyzed separately to account for the likelihood that a patient who undergoes RT or CRT might receive a higher radiation dose or other predisposing factors for a CVD, such as CT regimen, than those undergoing surgery alone. The age of 55 was used to divide the patients as young and old breast cancer patients according to the American Heart Association's scientific statement on cardiovascular risk factors. The independent variables were comorbidities, geographic area of residence, urbanization level, and socioeconomic status.

Statistical analysis

The SAS statistical package (version 9.2; SAS Institute, Inc., Cary, NC, USA) and SPSS (version 15, SPSS Inc., Chicago, IL, USA) were used to analyze the data. The cumulative risk of cardiovascular event was estimated as a function of time from initial treatment. Pearson Chi-square tests were used to explore the differences between categorical variables in the different treatment groups. Cardiovascular event-free survival rate was estimated using the Kaplan–Meier method, and the Cox proportional hazard regression model was used to calculate the relative risk of breast cancer patients between different treatment modalities after adjusting for the aforementioned variables. A p value less than 0.05 was considered statistically significant.

Results

For the 5514 breast cancer patients identified in this study, the median follow-up duration was 5.3 years (interquartile range 5–5.7 years). The mean age of the entire cohort was 51 years (standard deviation 12 years). A total of 1914 (35%) patients underwent surgery alone, 580 (10%) patients received RT, 1708 (31%) patients received CT, and 1312 (24%) patients received CRT. Table 1 presents the demographic characteristics of breast cancer patients according to different treatment modalities. Patients who underwent surgery alone were more likely to be older, to have lower Charlson Comorbidity Index Scores, to reside in Northern Taiwan, to be living in urban areas, and to have locoregional diseases.

At the end of the follow-up period, 289 patients were found to have CVD: 110 (5.7%) from the surgery-alone group, 24 (4.1%) from the RT group, 79 (4.6) from the CT group, and 76 (5.8%) from the CRT group. An interaction effect between CVD incidence and age groups was observed, and thus, the study cases were further stratified into four groups by age: less than 45 years old, 45–54 years old, 55–64 years old, and more than 65 years old (Table 2). Breast cancer patients who underwent CT and CRT at an age less than 55 years carried a higher risk of CVD when compared with the surgery-alone group (both groups $p < 0.001$; Table 3). There was no significant difference between the four groups at age 55 years or older. Figure 1 shows a significant difference in the increase in CVD risk for patients in the CT and CRT groups aged 55 or less with the p value less than 0.001. By contrast, breast cancer patients older than 55 years had no increasing risks of CVD between different treatment modalities.

Discussion

Our study shows that young breast cancer patients aged less than 55 years who undergo CT or CRT are at an increased risk of subsequent CVD. The hazard ratio of developing CVD among breast

Table 1
Demographic characteristics for breast cancer patients by different treatment modalities.

Variables	Surgery alone (n = 1914)	RT (n = 580)	CT (n = 1708)	CRT (n = 1312)	p
Age (y)					
<45	507 (26.5)	204 (35.2)	546 (32.0)	489 (37.3)	0.001
45–54	647 (33.8)	201 (34.7)	654 (38.3)	479 (36.5)	
55–64	357 (18.7)	96 (9.6)	314 (18.4)	238 (18.1)	
>65	403 (21.1)	79 (13.6)	194 (11.4)	106 (8.1)	
CCIS					
0–6	1499 (78.3)	344 (59.3)	929 (54.4)	324 (47.6)	<0.001
>6	415 (21.7)	236 (40.7)	779 (45.6)	688 (52.4)	
Enrollee category					
1–2	1094 (57.2)	306 (52.8)	920 (53.9)	771 (58.8)	0.026
3	654 (34.2)	228 (39.3)	648 (37.9)	451 (34.4)	
4	166 (8.7)	46 (7.9)	140 (8.2)	90 (6.9)	
Geographic region					
Northern	1125 (58.8)	303 (52.2)	892 (52.2)	629 (47.9)	
Central	425 (22.2)	139 (24.0)	403 (23.6)	386 (29.4)	<0.001
Southern	343 (17.9)	129 (22.2)	395 (23.1)	276 (21.0)	
Eastern	21 (1.1)	9 (1.6)	18 (1.1)	21 (1.6)	
Urbanization					
Urban	805 (42.1)	205 (35.3)	582 (34.1)	449 (34.2)	<0.001
Suburban	799 (41.7)	282 (48.6)	792 (46.4)	609 (46.4)	
Rural	310 (16.2)	93 (16.0)	334 (19.6)	254 (19.4)	
Tumor characteristics					
Locoregional	1899 (99.2)	507 (87.4)	1488 (87.1)	1191 (90.8)	<0.001
Distant metastasis	15 (0.8)	73 (12.6)	220 (12.9)	121 (9.2)	

Data are presented as n (%).
CCIS = Charlson Comorbidity Index Score; CRT = chemoradiotherapy ± surgery; CT = chemotherapy ± surgery; RT = radiotherapy ± surgery.

Table 2
Crude and adjusted hazard ratio of cardiovascular disease among breast cancer patients by age stratum in different treatment modalities.

Diagnosed age	RT vs. surgery alone				CT vs. surgery alone				CRT vs. surgery alone			
	Crude HR (95% CI)	p	Adjusted HR (95% CI)	p	Crude HR (95% CI)	p	Adjusted HR (95% CI)	p	Crude HR (95% CI)	p	Adjusted HR (95% CI)	p
<45	1.87 (0.78–4.52)	0.224	1.42 (0.72–2.64)	0.348	2.16 (0.82–5.70)	0.118	1.85 (0.68–5.04)	0.227	2.52 (0.96–6.64)	0.061	2.13 (0.78–5.81)	0.139
45–54	2.62 (0.91–7.55)	0.075	2.48 (0.85–7.17)	0.095	3.94 (1.80–8.61)	0.001	4.01 (1.82–8.83)	0.001	5.98 (2.75–13.0)	<0.001	6.15 (2.77–13.63)	<0.001
5564	0.94 (0.39–2.27)	0.882	0.75 (0.30–1.90)	0.545	0.93 (0.52–1.69)	0.816	0.84 (0.45–1.56)	0.571	0.75 (0.39–1.51)	0.413	0.72 (0.35–1.48)	0.368
>65	1.01 (0.55–1.86)	0.979	1.06 (0.57–1.98)	0.857	0.60 (0.36–1.01)	0.053	0.82 (0.48–1.41)	0.473	1.49 (0.91–2.43)	0.109	2.16 (1.27–3.69)	0.005
All patients	0.77 (0.50–1.20)	0.246	0.97 (0.62–1.51)	0.882	0.87 (0.65–1.17)	0.359	1.24 (0.92–2.53)	0.161	1.14 (0.85–1.53)	0.359	1.84 (1.34–2.53)	<0.001

Adjusted variables were the patients' age at diagnosis, sex, Charlson Comorbidity Index Score, socioeconomic status, urbanization of residence, and geographic region of residence.
95% CI = 95% confidence interval; CRT = chemoradiotherapy ± surgery; CT = chemotherapy ± surgery; HR = hazard ratio; RT = radiotherapy ± surgery.

Table 3
Crude and adjusted hazard ratio of cardiovascular disease among the breast cancer patients by treatment modality between young and old age groups.

Treatment modality	Age < 55 y					Age ≥ 55 y				
	CVD/Total (%)	Crude HR (95% CI)	p	Adjusted HR (95% CI)	p	CVD/Total (%)	Crude HR (95% CI)	p	Adjusted HR (95% CI)	p
Surgery alone	14/1154 (1.2)	Reference	—	Reference	—	96/760 (12.6)	Reference	—	Reference	—
RT	6/405 (1.5)	1.30 (0.50–3.39)	0.590	1.30 (0.50–3.39)	0.594	18/175 (10.3)	0.90 (0.54–1.49)	0.677	0.98 (0.89–1.64)	0.944
CT	42/1200 (3.5)	3.14 (1.72–5.75)	<0.001	3.00 (1.63–5.54)	<0.001	37/508 (7.3)	0.63 (0.43–0.92)	0.018	0.88 (0.59–1.32)	0.541
CRT	44/968 (4.5)	4.24 (2.32–7.73)	<0.001	4.22 (2.27–7.83)	<0.001	32/344 (9.3)	0.86 (0.57–1.28)	0.449	1.33 (0.86–2.05)	0.198

Adjusted variables were the patient's age at diagnosis, sex, socioeconomic status, urbanization of residence, and geographic region of residence.
95% CI = 95% confidence interval; CRT = chemoradiotherapy ± surgery; CT = chemotherapy ± surgery; CVD = cardiovascular disease; HR = hazard ratio; RT = radiotherapy ± surgery.

cancer patients aged less than 55 years who received CT is three times higher in patients receiving surgery alone, and 4.22 times higher in patients receiving CRT after adjusting for other factors. The incidence of CVD was much higher in patients older than 55 years of age regardless of treatment modalities. Similar results were seen in the Kaplan–Meier plot with the p value set at less than

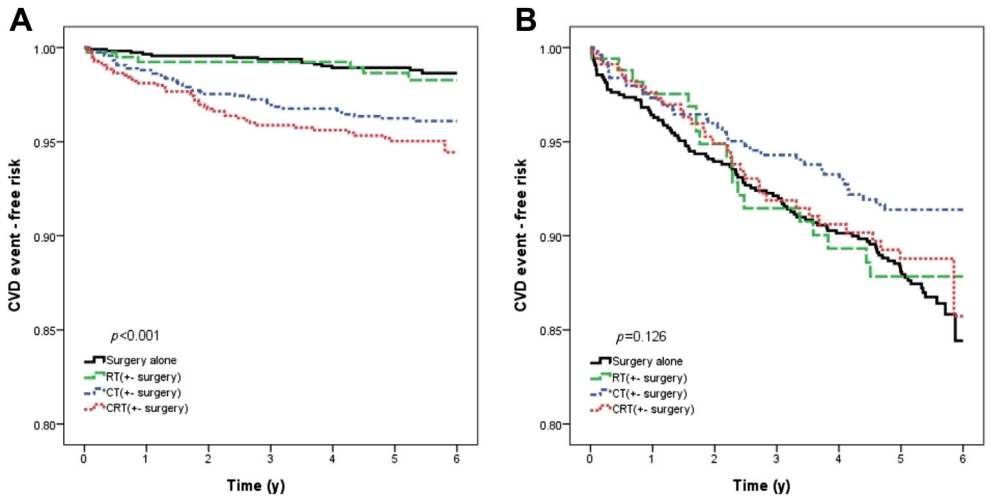

Figure 1. Cardiovascular event-free risk over time by treatment groups in breast cancer in patients aged (A) less than 55 and (B) more than 55 years. CT = chemotherapy ± surgery; CVD = cardiovascular disease; RT = radiotherapy ± surgery; CRT = chemoradiotherapy ± surgery; + − surgery = with or without surgery.

0.001 for patients aged less than 55 years. Our study adds several interesting points of information to existing knowledge on the incidence of CVD among breast cancer patients. Using a population-based dataset, the incidence of CVD increased more in the CT and/or CRT group rather than in the RT group alone in breast cancer patients younger than 55 years of age at the time diagnosis of the disease.

Breast cancer is treated with a multidisciplinary approach involving surgery, radiation oncology, and CT, which has been associated with a reduction in breast cancer mortality [12]. Anticancer therapies have led to a long life expectancy; however, because cardiac toxicity is one of most serious potential side effects, the gain in life expectancy due to anticancer therapy might be countered by an increased mortality due to cardiac problems, heart failure, myocardial ischemia, arrhythmias, hypertension, and thromboembolism [13]. A wide range of CT agents has been associated with cardiotoxicity. The anthracyclines (doxorubicin, daunorubicin, idarubicin, and epirubicin) are the most frequently implicated agents associated with cardiotoxicity, which are the commonly used regimen in breast cancer treatment [14]. In a meta-analysis of eight trials comparing an anthracycline-containing versus a nonanthracycline-containing CT regimen, use of anthracyclines was associated with a significantly increased risk of both clinical [odds ratio (OR) 5.43, 95% confidence interval (CI) 2.34–12.62] and subclinical cardiotoxicity (OR 6.25, 95% CI 2.58–15.13) [15]. Cardiac toxicity of anthracyclines involves oxidative stress and apoptosis [16]. Therefore, it is logical to hypothesize that using anthracycline as the main CT or CRT regimen might play a larger part in increasing CVD risk, compared with using only a surgical approach.

In addition, the Her-2-positive breast cancer patients are routinely treated with trastuzumab in Taiwan at present. Heart failure, a serious side effect, occurs in 1–4% of patients treated with trastuzumab, and 10% of patients have been observed to have a decrease in cardiac function [17]. Moreover, the combination of anthracyclines and trastuzumab in CRT appears to increase the incidence of cardiac side effects, which mediates cardiac failure in a direct, dose-dependent manner. Therefore, many clinical trials have been carried out on this topic to evaluate the treatment effects of trastuzumab. The Herceptin Adjuvant trial [18] focused on early breast cancer and showed that cardiac end points were higher in the trastuzumab group compared with observation (severe congestive heart failure, 0.60% vs. 0.00%; symptomatic congestive heart failure, 2.15% vs. 0.12%; confirmed significant left ventricular ejection fraction drops, 3.04% vs. 0.53%) [18]. Subsequently, a similar-designed study with a long-term follow-up (median 3.6 years) showed that the incidence of cardiac end points remained low, although it was higher in the trastuzumab group than in the observation group [19]. Concerning the late-stage metastatic breast cancer patients, the Herceptin, Cyclophosphamide, and Epirubicin trial evaluated the effect of trastuzumab plus cyclophosphamide and the less cardiotoxic anthracycline epirubicin on the dose-limiting cardiotoxicity. In that trial, the trastuzumab arm had a higher level of manageable cardiac adverse effects [20]. The underlying mechanisms may be revealed by the Her-2-deficient mouse model. The induction of cardiac stress pathways by either hemodynamic overload or the cardiotoxicity of anthracyclines promotes the onset of left ventricular dysfunction due to the action of ErbB2–ErbB4 heterodimeric receptors, which are important in triggering the myocyte-survival pathways [21,22]. These studies [21,22] support a two-hit model of trastuzumab cardiotoxicity, in which there is a loss of ErbB2-mediated pathways that normally blunt the effects of stress-signaling pathways activated by anthracyclines in the heart.

In our series, there was no statistical difference between the CVD incidence and treatment modalities in breast cancer patients aged 55 years and above. One of the most possible mechanisms is that increased competing mortality in older breast cancer patients masks the risk of CT and CRT. Breast cancer patients may die of index cancer and other conditions, such as sepsis, pneumonia, or stroke. Compared with younger breast cancer patients, older patients tend to have more comorbidities, an independent predictor of competing mortalities. Older patients may die of cancer or competing mortality prior to CVD manifestation. Another reason may be related to the myocardium injury, degeneration of endothelium, and adventitial fibrosis resulting from CT or CRT [8]. This effect is especially significant in young breast cancer patients aged between 45 years and 54 years. A similar phenomenon highlighting those young patients who developed a more severe atherosclerotic response than the reference group has already been reported [23]. In animal studies, the wound repair process becomes slower with advancing age and these age-related changes in the wound-repairing process might partially explain our results. However, further studies are necessary to explore the

precise mechanisms for the effect of age on CVD after systemic therapy for breast cancer.

RT, a critical component in breast-conserving therapy for breast cancer patients, has been evolving dramatically over the past several decades [24]. Although the association between breast cancer and ischemic heart disease has been discussed in numerous studies, several contrasting reports have also been published in recent years [3–7]. In a previous meta-analysis, breast cancer patients receiving RT in clinical trials have had significant excess mortality from heart disease (rate ratio 1.27, $p < 0001$) [25]. However, caution must be exercised when extrapolating the results of this meta-analysis, which included older trials using outdated radiation techniques to estimate risks for patients treated in the modern era [26]. A large population-based analysis, based on data in the SEER registries, of women treated for breast cancer from 1973 to 1989 suggested that the increased risk of ischemic heart disease associated with RT has decreased over time [27]. A single-institution retrospective review of cardiovascular death rates in patients treated with postmastectomy radiation between 1975 and 1994 documented very low rates of death from myocardial infarction [28]. Still, another SEER-based study found breast cancer survivors to have a diminished risk of acute myocardial infarction requiring hospitalization [29]. However, it is difficult to determine whether the low rate of events in these series simply reflects a lower baseline risk of ischemic cardiac disease in the breast cancer patient population, or whether it truly indicates that RT administered during that period had little effect on related risk. In fact, cardiac perfusion defects have been reported in patients treated from 1998 to 2002 [30], but the clinical consequences of these changes in cardiac perfusion are not yet clear. Another issue with treating breast cancer and CVD with RT involves the side treated by RT (i.e., right- or left-sided treatment). In 1979, the hazard ratio for women with left-sided treatment was 1.5, but the hazard of death from ischemic heart disease decreased by 6% with each succeeding year [31]. When investigators compared cardiac morbidity in breast cancer patients from 1986 to 1993 in another SEER-based study, they found no significant differences in rates of hospitalization for ischemic heart disease, valvular heart disease, conduction abnormalities, or heart failure [8]. By the 1980s, most radiation oncologists had abandoned cobalt units and outdated techniques such as deep tangents and *en face* "hockey stick" fields and began to routinely treat breast cancer patients with standard tangents using megavoltage linear accelerators [26]. In more recent years, some centers also began to use three-dimensional CT-based planning for left-sided breast cancers, which is particularly useful for minimizing cardiac irradiation [26,32].

The strength of our study is using the nationwide population-based cohort databank for analysis. The large number of study patients may reduce some selection bias. However, there are still several limitations in this study that should be highlighted. First, the diagnosis of breast cancer, CVD, and any other comorbid conditions is completely dependent on ICD codes. Nonetheless, the National Health Insurance Bureau of Taiwan randomly reviews the charts and interviews patients to verify the accuracy of diagnosis. The breast cancer patients are further verified by the registry for the catastrophic illness patient database. Second, the regimen of CT, dose and type of RT, and the severity and territory of the CVD cannot be precisely extracted from the NHIRD, which prevented further subgroup analysis. For example, trastuzumab, a recombinant humanized monoclonal antibody, which targets the Her-2 and inhibits carcinoma cellular proliferation mentioned earlier [33], was reported by Piotrowski et al [34] to have a higher incidence of cardiac complications. Tamoxifen and other selective estrogen receptor modulators reduce levels of plasma cholesterol and homocysteine but increase the level of serum triglyceride [35–37] and were associated with higher rates of venous thromboembolic disease and stroke [38]. Finally, further research linking primary hospitalization or ambulatory settings information such as types of CVD, severity, and detailed risk factors is worthy of future investigation.

In conclusion, breast cancer patients receiving CT and/or CRT have a higher risk of CVD, especially younger patients (aged < 55 years). Therefore, regular examinations of cardiac functions and electrocardiogram should be considered in cases of young breast cancer patients who are receiving CT and/or CRT.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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